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Primary HIV Infection: Clinical Presentation, Testing, and Treatment

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Abstract
Purpose of Review The purpose of this review was to provide current data on clinical presentation, diagnosis, and treatment of primary HIV infection (PHI).
Recent Findings In 65 to 95% of cases, PHI causes acute retroviral syndrome presenting with unspecific flu-like symptoms. Symptomatic PHI was associated with a faster clinical and immunological progression of HIV infection. Point-of-care tests remain less sensitive than fourth-generation immunoassays (IA) in PHI, especially after tenofovir-based prophylaxis use. Early antiretroviral treatment (ART) started during PHI prevents HIV transmission and decreases viral and immunological reservoir constitution. Recommended ART regimens in PHI are combinations of tenofovir and emtricitabine with either darunavir/ritonavir, or dolutegravir.
Summary Starting ART the earliest is highly recommended for clinical, virological, immunological, and public health benefits. Reducing HIV reservoir constitution in PHI may optimize potential opportunities for future functional cure.

Keywords Primary HIV infection · Acute retroviral syndrome · Fiebig stages · HIV diagnosis · Point-of-care tests · Antiretroviral treatment

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Introduction

In 2015, the United Nations estimated that 36.7 million people worldwide were living with human immunodeficiency virus (HIV) infection and that 2.1 million people had been newly infected [1].

Primary HIV infection (PHI) is defined as the 6 to 12 weeks between HIV exposure and the appearance of anti-HIV-antibodies, while acute HIV infection (AHI) starts with HIV plasma ribonucleic acid (RNA) detection and terminates when anti-HIV-antibodies appear.

During the few weeks following exposure, HIV replicates exponentially, rapidly seeding cell-associated viral reservoirs. As transmission is correlated with viral load [2], subjects with PHI are highly infectious regarding HIV transmission, all the more since they are unaware of their HIV-infected status. Hence, the risk of HIV transmission per sexual act is 10- to 26-fold higher in subjects with PHI than in individuals with chronic infection [3–5]. Modeling estimates suggest that acute and early HIV infections account for 38 to 50% of all forward transmission [6, 7]. Therefore, improving diagnosis and promoting early antiretroviral therapy in the primary stage of HIV infection are essential.

The aim of this review is to summarize the current knowledge about primary HIV infection, through its clinical, immune, viral, and therapeutic aspects.

Clinical Presentation

PHI is responsible for a flu-like illness known as acute retroviral syndrome (ARS) in 65 to 95% of patients [8–10,11••], which occurs just before or during the peak of viremia [11••].

The most frequent signs and symptoms are fever, headache, malaise, cough, and lymphadenopathy [11••]. Fatigue, myalgia, weight loss, night sweat, skin rash, pharyngitis, gastro-intestinal symptoms, aseptic meningitis, and oral or genital ulcers have also been reported (Supplementary material 1). Leukopenia, thrombocytopenia, and elevation of liver enzymes are present in one third to half of cases [12].

Two clinical points deserve special attention. First, neurological involvement, including aseptic meningitis, encephalitis, and facial nerve paresis, is reported in 14 to 25% of patients with ARS [9, 12]. Clinicians should be aware of the eventuality of a neurological presentation revealing a PHI. Secondly, ARS can rarely (< 10% cases) be associated with category B or C of the CDC classification symptomatic conditions, such as oral or esophageal candidiasis, gastro-intestinal or hepatic cytomegalovirus infection, multi-segmental herpes zoster, or peripheral polyneuropathy [13].

ARS is self-limited, resolves after 1 to 3 weeks (extremes from 5 to 44 days) [8, 10, 12], but appears to be a prognostic marker in HIV progression. Untreated subjects with ARS undergo a faster CD4 T cell decline and progression to AIDS than subjects with asymptomatic PHI [14]. The 12-month disease progression rate has also been shown to be higher in untreated PHI patients with ARS compared to asymptomatic PHI on a combination of both clinical and biological criteria (CD4 T cells count < 350/mm^3, or the occurrence of B or C clinical event in the CDC classification, or death) [8].

Biological Diagnosis Principles

After HIV exposure, local infection is established at transmission sites, and the virus spreads to regional lymph nodes and disseminates. Exponential HIV replication follows, leading to a peak in plasma HIV viral load (median 6.7 log copies per milliliter) about 13 days after HIV-RNA detectability (i.e., 2–3 weeks after infection) [11••]. The peak in genital viral load occurs about 30 days after infection [15]. Then, HIV-specific immune response leads to a decrease of viremia, and viral load reaches a set point (median 4.3 log copies per milliliter) about 5 weeks after infection [11••].

Natural History

Approximately 10–11 days after infection (range 8–17 days), HIV-1 RNA is detectable by nucleic acid testing (NAT) in plasma. Next, HIV-1 p24 antigen becomes detectable 14–15 days after infection. However, p24 antigen detection is transient, as when anti-HIV-1 antibodies appear, they bind to the p24 antigen and form immune complexes that interfere with p24 assay detection. This might lead to a "second window period", when p24 antigen is not detectable due to the formation of immune complexes, and HIV-antibodies are below the detection threshold. Immunoglobulin (Ig) M antibodies are expressed and can be detected by 21 to 42 days after infection. Finally, IgG antibodies develop and persist throughout the course of HIV infection [16•, 17••, 18].

The pattern of emergence of laboratory markers is highly consistent and allows classification of HIV infection into distinct laboratory stages [16•, 17••, 18] (Fig. 1; Table 1).

- The *eclipse period* is the initial interval after infection with HIV when no laboratory markers are detectable (from day 0 to day 11)
- The *seroconversion window period* is the interval between infection with HIV and the first detection of antibodies (from day 0 to day 21, maximum day 42)
- *Acute HIV infection (AHI)* is the interval between the appearance of detectable HIV RNA and the first detection of antibodies (from day 11 to day 21, maximum day 42). The evolution of virological laboratory markers was precisely described by Fiebig et al. [17••] (Table 1).
- *Established HIV infection* is the stage characterized by a fully developed IgG antibody response sufficient to meet the interpretive criteria for a positive Western blot (from 1-month post-infection).

According to the Center for Diseases Control [16•] and the European guidelines [19••], laboratories should conduct initial testing with a fourth-generation IA (which detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen) to screen for established infection with HIV-1 or HIV-2 and for AHI. The performances required for this screening test are a sensitivity of 100% and a specificity of 99.5%. No further testing is required for nonreactive specimens if there is no suspicion of AHI. All reactive specimens must undergo supplemental testing with a confirmation test.

Screening Diagnostic Tests

The sensitivity of fourth-generation IAs for established HIV-1 and HIV-2 infection ranges from 99.7 to 100% and their specificity from 99 to 100% [16•, 20]. However, they perform less in AHI than in established HIV-1 infection. Their sensitivity was 54–83% in patients with AHI who were negative by HIV-1 Western blot but reactive by HIV-1 NAT [16•, 21]. In a comparative study of FDA-labeled HIV-screening tests on sequential sera of patients with PHI, fourth-generation IAs were positive 5.3 to 7.4 days after HIV-RNA and 13 to

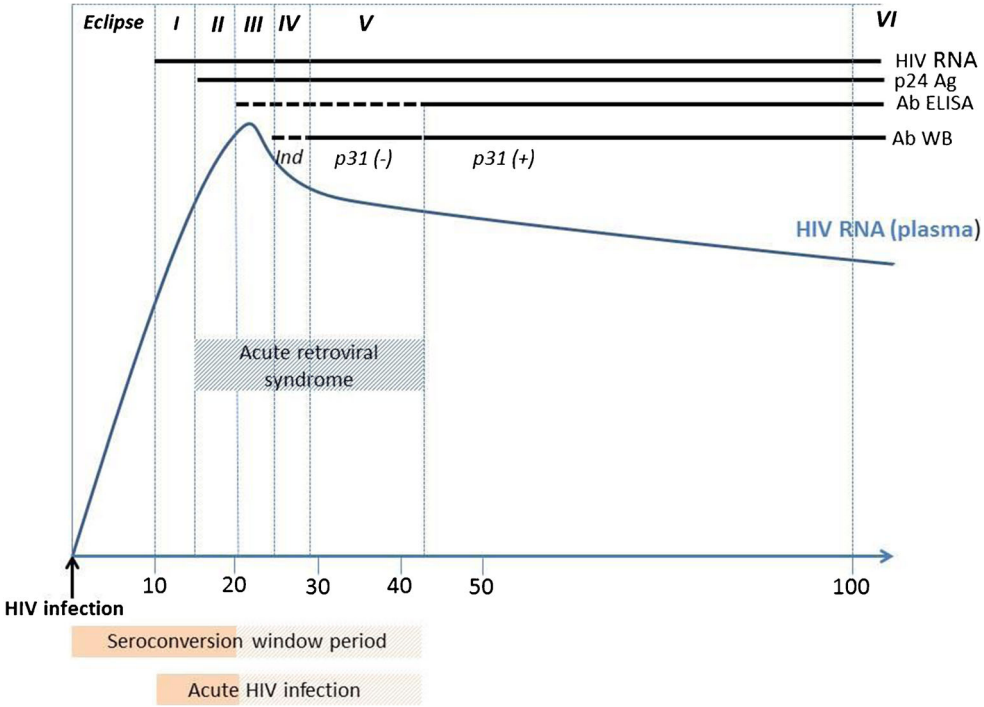

Fig. 1 Schematic display of the progression of HIV markers during primary HIV infection classified by Fiebig et al. [17]

23.6 days (median 17.8) after infection. The authors estimated by a simulation model that 99% of HIV-infected persons would be detectable by fourth-generation IAs within 45 days of exposure [22].

Therefore, to take in account the inter-individual variable delay before development of antibodies, the lower sensitivity of screening tests for AHI than for established infection and the possible negativity of p24 antigen when antibodies develop, a fourth-generation IA formally excludes HIV infection if performed at least 6 weeks after exposure. In case of negative fourth-generation IA with suspicion of symptomatic PHI, an HIV viral load should be performed.

Confirmation Tests

A positive screening test requires a confirmation test: a HIV-1/HIV-2 antibody differentiation assay (ADA) in the USA, a Western blot (WB) or an immunoblot in Europe. In addition, according to the CDC, specimens which are reactive on the initial fourth-generation IA and nonreactive or indeterminate on the ADA proceed to HIV-1 NAT to distinguish acute HIV-1 infection from false-positive initial IAs results.

Interpretation of Western Blot

The WB is interpreted as positive, negative, or indeterminate, depending on the number and specificity of the positive bands, revealing the presence of antibodies to HIV-1 antigens (Supplementary material 2).

However, WB has limitations: its results are negative or indeterminate early in the course of HIV infection, and HIV-2 infections may be misclassified as HIV-1 by the HIV-1 WB [23]. Three alternative confirmation tests might overcome these limitations: the antibody differentiation assay (ADA), a specific HIV-2 WB, and the HIV1 NAT.

Table 1 Fiebig stages: laboratory stages of primary HIV-1 infection based on the emergence of viral markers

Stage	Time from infection (days)	RNA	p24 antigen	IgM antibodies (fourth generation EIA)	Western blot
I	11	+	−	−	−
II	14	+	+	−	−
III	21	+	+	+	−
IV	25	+	+/−	+	I
V	28	+	+/−	+	+ p31 band (−)
VI	100	+	+/−	+	+ p31 band (+)

RNA ribonucleic acid, *EIA* enzyme immunoassay, *I* indeterminate

The HIV-1/HIV-2 Antibody Differentiation Assay

ADA is the confirmation test recommended in the USA. It is a rapid, qualitative immunoconcentrating assay that detects and differentiates antibodies against HIV-1 and HIV-2. Sensitivity of the ADA for established HIV-1 ranges from 98.5 to 100%, and specificity is 99%. In acute HIV-1 infection, the ADA was positive 7 days earlier than the WB and reduced indeterminate results [24].

The HIV-2 WB

A negative or indeterminate HIV-1 WB after a positive fourth-generation IA might indicate either an early infection, or an HIV-2 infection, or a false-positive. A control of HIV-1 WB 14 days later associated with a specific HIV-2 WB concludes on the definite result (Supplementary material 2).

HIV-1 NAT

HIV-1 NAT is the earliest positive test during PHI (11 days after infection), with a sensitivity of 100%. However, it is less specific (2–5% false-positive), more time-consuming, and more expensive than other diagnostic tests [25]. Its indications are limited to specimens that are reactive on the initial IA and nonreactive or indeterminate on confirmation tests.

Point-of-Care Tests

Disadvantages of the reference diagnostic method include the need for venipuncture and the requirement of a follow up visit, while up to half of the tested persons do not return to receive their HIV test results [26]. Point-of-care tests (POCTs), also known as rapid disposable tests, have been developed to increase access to HIV-screening and reduce barriers to early diagnosis of HIV infection (Supplementary material 3). To be performed outside laboratories, they use direct, unprocessed specimens (finger-stick capillary whole blood or oral fluid) but some are also available for plasma or serum. Results are available within 30 min of testing. These POCTs are based on immunofiltration or immunochromatography: HIV-1 and HIV-2 synthetic antigens are affixed to the test strip or membrane, and if the specimen contains HIV-antibodies, the binding of HIV-antibodies to the antigen results in a colorimetric reaction.

POCTs detect HIV-antibodies but not p24 antigen (except the Determine® HIV-1/2 Ag/Ab Combo®), and become positive between 21 days and up to 42 days following HIV infection.

Sensitivity of POCTs for established HIV infection is ≥ 98% with specificity around 99%. In AHI, POCTs on whole blood and even more on oral fluid, lack sensitivity [27, 28]. In a prospective study in men who have sex with men in the USA, the POCT OraQuick® identified 91% of HIV-antibody-positive patients. Most of the Ora-Quick® negative, EIA-positive patients had early infection [29]. In another study, the sensitivity in 53 patients with recent HIV infection was 88.5% for EIA, 79.2% for the POCT on oral fluid, and 81.1% to 88% for the POCTs on whole blood [30].

There are a number of reasons for this. First, all but one POCTs detect antibodies and not p24 antigen; so their detection window is at least 21 days—longer than the 14–15 days detection window with a fourth-generation IA. Secondly, the dilution of whole blood compared to serum, and the low concentration of antibodies in oral fluid might contribute to the decreasing sensitivity of diagnostic tests on whole blood and oral fluid compared to serum [28]. At last, the short migration or filtration time for antigen-antibody binding and a weaker antibody affinity due to hemolysis and reaction at room temperature instead of 37 °C have also been suggested [28].

In pre-exposure prophylaxis (PrEP) settings which involve frequent HIV testing, POCTs on whole blood reveal less sensitivity compared to antigen/antibody tests [31]. PrEP with tenofovir in injecting drugs users has also been associated with a higher risk of false-negative results of oral POCT compared to patients receiving placebo in Thailand [32]. However, this was not confirmed on two other PrEP trials analyzed by the same authors [32].

The Determine® HIV-1/2 Ag/Ab Combo® test was an attempt to improve the diagnosis of early HIV infection. Unfortunately, its sensitivity for the detection of p24 antigen is much lower than for the detection of antibodies [28, 33, 34], and it did not perform better than other POCTs. Overall, in a recent meta-analysis, POCTs were less sensitive than fourth-generation IAs for the diagnosis of HIV infection in clinical settings, and this difference was stronger in high-income than in low-income countries, maybe as a result of a higher incidence of AHI [35]. The authors estimated that in high-income countries about one in seven HIV infections were missed by POCTs when they were used alone. Newer and more sensitive RNA/DNA-based POCTs are being developed and validated but are not available for now.

Overall current POCTs must not be used as the sole screening test in suspected PHI settings and should be completed by a fourth-generation IA.

A positive POCT must be confirmed by the reference diagnostic process, including a fourth-generation IA and a confirmation test with a WB or immunoblot in Europe [36] or an ADA in the USA [16].

Antiretroviral Treatment

Early antiretroviral treatment (ART) of PHI has demonstrated virological and immunological benefits and potential clinical benefits. The earlier the stage of PHI, the more important it is to start the treatment early [37].

Virological Benefits

Early ART in PHI lowers HIV-RNA viral load set point [38–40]. In 173 patients enrolled during PHI to receive either no treatment or 24 or 60 weeks of ART from baseline, the mean viral set point was measured 36 weeks after randomization in the untreated arm and 36 weeks after treatment interruption in the treatment arms. It was 4.8 log10 copies/mL (standard deviation (SD) 0.6) in the untreated arm, and 4.0 (SD 1.0) and 4.3 (SD 0.9) log10 copies/mL, respectively, in the 24- and 60-week treatment arms ($p < 0.001$) [39].

HIV establishes reservoir early in infection, rapidly replicating and seeding peripheral blood mononuclear cell (PBMC) and tissue sanctuary (gut and lymph nodes principally) in an integrated form [41]. With HIV plasma kinetics, there is a rapid seeding of the viral reservoir when evaluated by HIV DNA monitoring. HIV DNA set point is established early in PHI, around 4 weeks after infection [42]. Early ART dramatically reduces this set point. Among 90 Thai patients with early acute HIV infection, 71 received immediate ART while 19 were not treated. The total and integrated HIV DNA levels were closely monitored. The total DNA level in untreated patients was 20-fold higher than in treated patients at week 2 following enrollment, and 316-fold by week 144. For integrated DNA, the ratio was 25 by week 2 and 100 by week 144 [42]. The French cohort PRIMO, including patients with PHI, also showed that the earlier ART was initiated, the faster cell-associated HIV-DNA level decreased [43].

In addition, early treatment prevents colonic mucosal mononuclear cells infection. Among 41 patients with AHI who underwent a sigmoidoscopy at diagnosis, before starting ART, 10 had an undetectable HIV RNA in homogenized colon biopsy specimens. The median delay between HIV exposure and colon biopsy was 11 days in these patients, versus 16 days in the 31 participants with detectable HIV RNA in colon ($p = 0.02$). All but one patient received immediate ART after biopsy and underwent a measure of total HIV DNA in colonic mononuclear cells after 24 weeks of ART. Participants with baseline detectable colonic HIV RNA demonstrated persistent elevation in total HIV DNA in colonic mucosal mononuclear cells, while it was undetectable in the 10 patients with undetectable HIV RNA in biopsy at baseline [44].

Virologic failure is uncommon after treatment initiation during PHI: of 264 Thai patients treated during AHI, only 1.1% did not achieve HIV RNA less than 200 copies/mL at 24 weeks [45]. Participants who initiated ART during Fiebig I stage demonstrated a shorter median time to virological suppression (8 weeks, interquartile range (IQR) 4–12) than did all other stages combined (12 weeks, IQR 8–16, $p < 0.001$) [45].

Between 5 and 15% of HIV-1-infected patients treated early during PHI, also known as post-treatment controllers, maintain viral suppression after stopping ART [46–51]. However interruption of ART is not recommended because in most cases it has a negative impact on CD4 cell recovery [52], inflammation [53], and risk of AIDS and non-AIDS events in chronic HIV-1 infection [54].

Immunological Benefits

PHI is associated with an important immune activation consistent with cytokine release which amplifies viral replication in lymphoid organs [55]. Early treatment in PHI reduces immune activation and inflammation and decreases systemic inflammatory biomarkers [56]. Early ART also preserves immune function [57–61] and integrity of lymphoid tissue [62, 63] and enhances CD4 T cell recovery [64, 65]. Whereas CD4/CD8 cell ratio declines rapidly during untreated PHI, initiation of ART within 40 days of the estimated date of infection significantly increases the CD4/CD8 ratio [66].

Treatment of PHI may reduce HIV-induced inflammation in the central nervous system. In the first study, cerebrospinal fluid (CSF) neurofilament light chain (NFL), a measure of axonal injury, was above the normal value in 1 of 32 (3.1%) acutely HIV infected patients and in 10 of 32 (31%) chronically HIV infected patients ($p = 0.006$). The difference persisted after 6 months of ART [67]. However, in a second study, nine patients who started ART in the 4 months after infection had lower interleukin six levels in CSF, but no difference for Global Deficit Score, NFL, or HIV DNA detectability compared to seven patients who started ART >14 months after infection [68].

Very early after HIV infection (in Fiebig I and II stages), there is substantial depletion of CD4+ T cells in the gastrointestinal tract lamina propria (LP), with associated epithelial barrier damage, leading to microbial translocation, systemic inflammation and immune activation [69]. In the Thai cohort of acute HIV-infected patients, there was resolution of gastrointestinal tract inflammation (determined by the numbers of cells that were expressing the proinflammatory cytokine TNF-α in the LP) and immune activation (assessed by the number of Ki-67+ cells in the LP) back to baseline levels after 96 weeks of ART. However, they did not recover gastrointestinal tract damage with microbial translocation (measured by neutrophil infiltration) nor CD4+ T cells level in the LP after 96 weeks of ART [69].

Early ART in PHI is associated with immune restoration and reduced reservoir size [63, 70, 71, 72••] and may favor post-treatment control [46, 51], thereby enhancing research on strategies to achieve HIV drug-free remission. Therefore, early treatment in PHI is a critical step in any pathway toward an HIV cure [73].

Clinical Benefits

Clinical trial data regarding the clinical benefit treatment of ART in PHI are limited. Many individuals enrolled in studies

to assess the role of ART in early HIV-1 infection were identified as trial participants because they presented with signs or symptoms of acute infection. Nevertheless, treatment in PHI appeared to limit the evolution to advanced B and C CDC stages [74] and to reduce both AIDS and non-AIDS morbidity and mortality [66].

In addition, ART started in symptomatic PHI might reduce severity of acute symptoms. Moreover, depression and anxiety, which are common at PHI diagnosis, may be improved by the initiation of ART [75].

As with chronic infection, patients with early HIV-1 infection must be willing and able to commit to treatment. On a case-by-case basis, providers may recommend that patients defer therapy for clinical and/or psychosocial reasons. If treatment during early infection is deferred, patients should be maintained in care and every effort should be made to initiate therapy as soon as they are ready [76••].

Public Health Benefits

Early HIV-1 infection is associated with high viral loads and increased infectiousness [4, 77, 78], and ART-use by HIV-1-infected individuals reduces transmission to uninfected sexual partners, especially during PHI [79, 80]. Early ART is consistent with the principle of Treatment-as-Prevention (TasP) which refers to the use of ART to reduce the amount of virus in patients' blood (and genital fluids) to decrease the risk of HIV transmission [81].

In order to decrease the overall HIV burden, people living with HIV should be diagnosed as early as possible after acquiring HIV infection, so that they can be linked to prevention and treatment services, and ART can be initiated.

Furthermore, knowledge of HIV-positive status modifies sexual behavior, especially toward more frequent condom use, limiting the risk of transmission [82, 83].

ART Choice

Treatment choice should follow international guidelines and should be based on the local epidemiology of resistance. ART must be started as soon as possible in PHI, especially in case of an symptomatic acute infection, severe or prolonged symptoms, neurological disease, age > 50 years, and CD4 count < 350 cells/μL [19••].

The treatment should include a combination of two nucleoside reverse transcriptase inhibitors (NRTI), namely tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), associated with emtricitabine (FTC). Abacavir is not recommended for empiric treatment of acute infection unless the patient is known to be HLA-B*5701 negative.

Because it is important to start the treatment immediately in acute infection, without waiting for the results of antiretroviral drug resistance testing, the third agent should have a high genetic barrier to resistance. The high genetic barrier to resistance is a cornerstone, as the virus may be resistant to at least one antiretroviral drug in up to 16% of patients in the USA [84], 8.2% in recent years in Italy [85] or 4.8% in Thailand during PHI in 2013–2014 [86], and up to 16.3% (95%CI 8.1–30.0%) in 43 acute or early HIV infections in Brazil [87]. The third agent must be chosen among either a pharmacologically boosted protease inhibitor (PI), namely darunavir 800 mg (DRV) boosted with ritonavir or cobicistat, or an integrase inhibitor (INI) namely dolutegravir 50 mg (DTG) [19••, 76].

Some authors reported the use of tenofovir/emtricitabine/elvitegravir/cobicistat as a single tablet regimen during PHI in 23 patients with virological efficacy and safety [88] and in 6 patients, with early and sustained virological response and decrease in HIV DNA [89]. However, the number of patients included in these trials is too limited to propose this treatment for now.

Intensification trials with the addition of maraviroc and raltegravir [71, 90], or only maraviroc [91, 92] to standard treatment of PHI, are not recommended, as they did not significantly improve virological control nor long-term immunological recovery.

Whenever possible, the inclusion of subjects with PHI in clinical trials or studies investigating HIV curative strategies is desirable.

The treatment may be changed if necessary after the results of resistance testing.

The goal of ART is to obtain a viral load < 50 copies/mL after 6 months of treatment, but undetectability may take up to 1 year if the initial viral load is high [36].

The healthcare provider should discuss the diagnosis of PHI with the patient, explain why early treatment is recommended, and provide therapeutic education to ensure adherence to the treatment. ART started during PHI should be continued lifelong, as recommended for any HIV-infected person.

Patients should be also screened for other sexually transmitted diseases such as hepatitis B and C, syphilis, and *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection. Moreover, patients should be encouraged to inform their partners, in order to be tested for HIV and to start post-exposure prophylaxis with ART if appropriate, especially during the first months as patients with PHI have a detectable viral load several months after ART initiation.

Particular Cases

PrEP Users

A previous use of pre-exposure or post-exposure prophylaxis should also be established, as its failure could be predictive of a resistance to the prophylactic ART received. In case of PHI after the use of PrEP (TDF/FTC), the risk of infection with a resistant

strain exists [93], but remains exceptional. Therefore, it is still recommended to start initially a TDF/FTC-based treatment [76].

Chronic Kidney Damage

The fixed association of TDF/FTC is not recommended in patients with creatinine clearance lower than 60 mL/min. In subjects with creatinine clearance above 30 mL/min, TAF should be used instead of TDF. The combination of raltegravir and lamivudine (with dose adjustment to creatinine clearance) is recommended as initial treatment, along with darunavir and ritonavir for creatinine clearance below 30 mL/min [36].

Conclusion

Primary HIV infection may be a challenging diagnosis because of its unspecific flu-like symptoms. The diagnosis is based on fourth-generation immunoassay, as POCTs lack sensitivity in early infection. Treatment should be started, as soon as possible, to obtain clinical, virological, and immunological benefits, and in order to prevent further transmission.

Reducing the establishment of HIV reservoir in PHI by early ART may also optimize potential opportunities for viral eradication or functional cure in the future.

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Compliance with Ethical Standards

Conflict of Interest Dr. Henn declares receiving travel accommodations expensive covered and reimbursed by ViiV, Janssen-Cilag,MSD France.

Dr. Flateau declares receiving travel accommodations expensive covered and imbursed by ViiV, Janssen-Cilag,MSD France.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Global AIDS Update| UNAIDS [Internet] 2016. [cited 2017 Feb 22]. Available from: http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016
2. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. 2000;342:921–9.
3. Pilcher CD, Tien HC, Eron JJ, Vernazza PL, Leu S-Y, Stewart PW, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis. 2007;189:1785–92.
4. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis. 2005;191:1403–9.
5. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. J Infect Dis. 2008;198:687–93.
6. Powers KA, Ghani AC, Miller WC, Hoffman IF, Pettifor AE, Kamanga G, et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. Lancet. 2011;378:256–68.
7. Brenner BG, Roger M, Routy J-P, Moisi D, Ntemgwa M, Matte C, et al. High rates of forward transmission events after acute/early HIV-1 infection. J Infect Dis. 2007;195:951–9.
8. Socías ME, Sued O, Laufer N, Lázaro ME, Mingrone H, Pryluka D, et al. Acute retroviral syndrome and high baseline viral load are predictors of rapid HIV progression among untreated Argentinean seroconverters. J Int AIDS Soc. 2011;14:40.
9. Braun DL, Kouyos R, Oberle C, Grube C, Joos B, Fellay J, et al. A novel Acute Retroviral Syndrome Severity Score predicts the key surrogate markers for HIV-1 disease progression. PLoS One. 2014;9:e114111.
10. Hoenigl M, Green N, Camacho M, Gianella S, Mehta SR, Smith DM, et al. Signs or symptoms of acute HIV infection in a cohort undergoing community-based screening. Emerg Infect Dis. 2016;22:532–4.
11.•• Robb ML, Eller LA, Kibuuka H, Rono K, Maganga L, Nitayaphan S, et al. Prospective study of acute HIV-1 infection in adults in East Africa and Thailand. N Engl J Med. 2016;374:2120–30. **This study improves knowledge on the natural history of viral replication in early HIV infection**
12. Sun H-Y, Chen M-J, Hung C-C, Chen M-Y, Hsieh S-M, Sheng W-H, et al. Clinical presentations and virologic characteristics of primary human immunodeficiency virus type-1 infection in a university hospital in Taiwan. J Microbiol Immunol Infect. 2004;37:271–5.
13. Braun DL, Kouyos RD, Balmer B, Grube C, Weber R, Günthard HF. Frequency and spectrum of unexpected clinical manifestations of primary HIV-1 infection. Clin Infect Dis. 2015;61:1013–21.
14. Sinicco A, Fora R, Sciandra M, Lucchini A, Caramello P, Gioannini P. Risk of developing AIDS after primary acute HIV-1 infection. J Acquir Immune Defic Syndr. 1993;6:575–81.
15. Pilcher CD, Joaki G, Hoffman IF, Martinson FEA, Mapanje C, Stewart PW, et al. Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. AIDS. 2007;21:1723–30.
16.• Centers for disease control and prevention and association of public health laboratories. Laboratory testing for the diagnosis of HIV infection: Updated Recommendations . 2014. http://dx.doi.org/10.15620/cdc.23447. Accessed 8 Aug 2017. **The CDC HIV testing recommendations**
17.•• Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS. 2003;17:1871–9. **Describes the timepoints of appearance of HIV-1 markers and viral load concentrations during primary HIV infection. This study allowed the definition and estimation of the duration of six sequential stages, currently know as the "Fiebig stages"**

18. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. N Engl J Med. 2011;364:1943–54.
19.•• European AIDS clinical society. European guidelines for treatment of HIV-positive adults in Europe version 8.2: updated January 2017. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed 8 Aug 2017. **The European recommandations.**
20. Sickinger E, Jonas G, Yem AW, Goller A, Stieler M, Brennan C, et al. Performance evaluation of the new fully automated human immunodeficiency virus antigen-antibody combination assay designed for blood screening. Transfusion. 2008;48:584–93.
21. Pilcher CD, Louie B, Facente S, Keating S, Hackett J, Vallari A, et al. Performance of rapid point-of-care and laboratory tests for acute and established HIV infection in San Francisco. PLoS One. 2013;8:e80629.
22. Delaney KP, Hanson DL, Masciotra S, Ethridge SF, Wesolowski L, Owen SM. Time until emergence of HIV test reactivity following infection with HIV-1: implications for interpreting test results and retesting after exposure. Clin Infect Dis. 2017;64:53–9.
23. Nasrullah M, Ethridge SF, Delaney KP, Wesolowski LG, Granade TC, Schwendemann J, et al. Comparison of alternative interpretive criteria for the HIV-1 Western blot and results of the Multispot HIV-1/HIV-2 Rapid Test for classifying HIV-1 and HIV-2 infections. J Clin Virol. 2011;52(Suppl 1):S23–7.
24. Masciotra S, McDougal JS, Feldman J, Sprinkle P, Wesolowski L, Owen SM. Evaluation of an alternative HIV diagnostic algorithm using specimens from seroconversion panels and persons with established HIV infections. J Clin Virol. 2011;52(Suppl 1):S17–22.
25. Hecht FM, Busch MP, Rawal B, Webb M, Rosenberg E, Swanson M, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS. 2002;16:1119–29.
26. Sullivan PS, Lansky A, Drake A. HITS-2000 Investigators. Failure to return for HIV test results among persons at high risk for HIV infection: results from a multistate interview project. J Acquir Immune Defic Syndr. 2004;35:511–8.
27. Laforgerie E, Boucher B, Ly TD, Maisoneuve L, Izopet J, Delaugerre C, et al. Sensitivity of 8 CE (European Community)-approved rapid disposable tests for anti-HIV antibody detection during and after seroconversion. J Virol Methods. 2010;165:105–7.
28. Pavie J, Rachline A, Loze B, Niedbalski L, Delaugerre C, Laforgerie E, et al. Sensitivity of five rapid HIV tests on oral fluid or finger-stick whole blood: a real-time comparison in a healthcare setting. PLoS One. 2010;5:e11581.
29. Stekler JD, Swenson PD, Coombs RW, Dragavon J, Thomas KK, Brennan CA, et al. HIV testing in a high-incidence population: is antibody testing alone good enough? Clin Infect Dis. 2009;49:444–53.
30. Stekler JD, O'Neal JD, Lane A, Swanson F, Maenza J, Stevens CE, et al. Relative accuracy of serum, whole blood, and oral fluid HIV tests among Seattle men who have sex with men. J Clin Virol. 2013;58(Suppl 1):e119–22.
31. Delaugerre C, Antoni G, Mahjoub N, Pialoux G, Cua E, Pasquet A, et al. Assessment of HIV screening tests for pre-exposure prophylaxis programs. J Infect Dis. 2017. doi:10.1093/infdis/jix297.
32. Curlin ME, Gvetadze R, Leelawiwat W, Martin M, Rose C, Niska RW, et al. Analysis of false-negative human immunodeficiency virus rapid tests performed on oral fluid in 3 international clinical research studies. Clin Infect Dis. 2017;64:1663–9.
33. Smallwood M, Vijh R, Nauche B, Lebouché B, Joseph L, Pant PN. Evaluation of a rapid point of care test for detecting acute and established HIV infection, and examining the role of study quality on diagnostic accuracy: a Bayesian meta-analysis. PLoS One. 2016;11:e0149592.
34. van Tienen C, Rugebregt S, Scherbeijn S, Götz H, GeurtsvanKessel C. The performance of the Alere HIV combo point-of-care test on stored serum samples; useful for detection of early HIV-1 infections?. Sex Transm Infect. 2017. doi:10.1136/sextrans-2016-052818.
35. Tan WS, Chow EPF, Fairley CK, Chen MY, Bradshaw CS, Read TRH. Sensitivity of HIV rapid tests compared with fourth-generation enzyme immunoassays or HIV RNA tests. AIDS. 2016;30:1951–60.
36. experts-vih_primo-infection.pdf [Internet]. [cited 2017 May 25]. Available from: http://cns.sante.fr/wp-content/uploads/2017/01/experts-vih_primo-infection.pdf
37. Robb ML, Ananworanich J. Lessons from acute HIV infection. Curr Opin HIV AIDS. 2016;11:555–60.
38. Hogan CM, Degruttola V, Sun X, Fiscus SA, Del Rio C, Hare CB, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. J Infect Dis. 2012;205:87–96.
39. Grijsen ML, Steingrover R, Wit FWNM, Jurriaans S, Verbon A, Brinkman K, et al. No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: the randomized Primo-SHM trial. PLoS Med. 2012;9:e1001196.
40. Ananworanich J, Schuetz A, Vandergeeten C, Sereti I, de Souza M, Rerknimitr R, et al. Impact of multi-targeted antiretroviral treatment on gut T cell depletion and HIV reservoir seeding during acute HIV infection. PLoS One. 2012;7:e33948.
41. Kulpa DA, Chomont N. HIV persistence in the setting of antiretroviral therapy: when, where and how does HIV hide? J Virus Erad. 2015;1:59–66.
42. Ananworanich J, Chomont N, Eller LA, Kroon E, Tovanabutra S, Bose M, et al. HIV DNA set point is rapidly established in acute HIV infection and dramatically reduced by early ART. EBioMedicine. 2016;11:68–72.
43. Laanani M, Ghosn J, Essat A, Melard A, Seng R, Gousset M, et al. Impact of the timing of initiation of antiretroviral therapy during primary HIV-1 infection on the decay of cell-associated HIV-DNA. Clin Infect Dis. 2015;60:1715–21.
44. Crowell TA, Fletcher JL, Sereti I, Pinyakorn S, Dewar R, Krebs SJ, et al. Initiation of antiretroviral therapy before detection of colonic infiltration by HIV reduces viral reservoirs, inflammation and immune activation. J Int AIDS Soc. 2016;19:21163.
45. Crowell TA, Phanuphak N, Pinyakorn S, Kroon E, Fletcher JLK, Colby D, et al. Virologic failure is uncommon after treatment initiation during acute HIV infection. AIDS. 2016;30:1943–50.
46. Sáez-Cirión A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog. 2013;9:e1003211.
47. Goujard C, Girault I, Rouzioux C, Lécuroux C, Deveau C, Chaix M-L, et al. HIV-1 control after transient antiretroviral treatment initiated in primary infection: role of patient characteristics and effect of therapy. Antivir Ther. 2012;17:1001–9.
48. Lodi S, Meyer L, Kelleher AD, Rosinska M, Ghosn J, Sannes M, et al. Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion. Arch Intern Med. 2012;172:1252–5.
49. Martin GE, Gossez M, Williams JP, Stöhr W, Meyerowitz J, Leitman EM, et al. Post-treatment control or treated controllers? Viral remission in treated and untreated primary HIV infection. AIDS. 2017;31:477–84.
50. Fidler S, Olson AD, Bucher HC, Fox J, Thornhill J, Morrison C, et al. Virological blips and predictors of post treatment viral control after stopping ART started in primary HIV infection. J Acquir Immune Defic Syndr. 2017;74:126–33.
51. Hocqueloux L, Prazuck T, Avettand-Fenoel V, Lafeuillade A, Cardon B, Viard J-P, et al. Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. AIDS. 2010;24:1598–601.

52. Krastinova E, Seng R, Lechenadec J, Panjo H, Essat A, Makhloufi D, et al. Does transient cART started during primary HIV infection undermine the long-term immunologic and virologic response on cART resumption? BMC Infect Dis. 2015;15:178.
53. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008;5:e203.
54. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355:2283–96.
55. Stacey AR, Norris PJ, Qin L, Haygreen EA, Taylor E, Heitman J, et al. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections. J Virol. 2009;83:3719–33.
56. Sereti I, Krebs SJ, Phanuphak N, Fletcher JL, Slike B, Pinyakorn S, et al. Persistent, albeit reduced, chronic inflammation in persons starting antiretroviral therapy in acute HIV infection. Clin Infect Dis. 2017;64:124–31.
57. Hocqueloux L, Avettand-Fènoël V, Jacquot S, Prazuck T, Legac E, Mélard A, et al. Long-term antiretroviral therapy initiated during primary HIV-1 infection is key to achieving both low HIV reservoirs and normal T cell counts. J Antimicrob Chemother. 2013;68:1169–78.
58. Le T, Wright EJ, Smith DM, He W, Catano G, Okulicz JF, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. N Engl J Med. 2013;368:218–30.
59. Seng R, Goujard C, Krastinova E, Miailhes P, Orr S, Molina J-M, et al. Influence of lifelong cumulative HIV viremia on long-term recovery of CD4+ cell count and CD4+/CD8+ ratio among patients on combination antiretroviral therapy. AIDS. 2015;29:595–607.
60. Thornhill J, Inshaw J, Kaleebu P, Cooper D, Ramjee G, Schechter M, et al. Brief report: enhanced normalization of CD4/CD8 ratio with earlier antiretroviral therapy at primary HIV infection. J Acquir Immune Defic Syndr. 2016;73:69–73.
61. Chéret A, Bacchus-Souffan C, Avettand-Fenoël V, Mélard A, Nembot G, Blanc C, et al. Combined ART started during acute HIV infection protects central memory CD4+ T cells and can induce remission. J Antimicrob Chemother. 2015;70:2108–20.
62. Schuetz A, Deleage C, Sereti I, Rerknimitr R, Phanuphak N, Phuang-Ngern Y, et al. Initiation of ART during early acute HIV infection preserves mucosal Th17 function and reverses HIV-related immune activation. PLoS Pathog. 2014;10:e1004543.
63. Ananworanich J, Chomont N, Fletcher JL, Pinyakorn S, Schuetz A, Sereti I, et al. Markers of HIV reservoir size and immune activation after treatment in acute HIV infection with and without raltegravir and maraviroc intensification. J Virus Erad. 1:116–22.
64. SPARTAC Trial Investigators, Fidler S, Porter K, Ewings F, Frater J, Ramjee G, et al. Short-course antiretroviral therapy in primary HIV infection. N Engl J Med. 2013;368:207–17.
65. Ananworanich J, Sacdalan CP, Pinyakorn S, Chomont N, Souza M, Luekasemsuk T, et al. Virological and immunological characteristics of HIV-infected individuals at the earliest stage of infection. J Virus Erad. 2016;2:43–8.
66. Hoenigl M, Chaillon A, Little SJ. CD4/CD8 cell ratio in acute HIV infection and the impact of early antiretroviral therapy. Clin Infect Dis. 2016;63:425–6.
67. Peluso MJ, Valcour V, Ananworanich J, Sithinamsuwan P, Chalermchai T, Fletcher JLK, et al. Absence of cerebrospinal fluid signs of neuronal injury before and after immediate antiretroviral therapy in acute HIV infection. J Infect Dis. 2015;212:1759–67.
68. Oliveira MF, Chaillon A, Nakazawa M, Vargas M, Letendre SL, Strain MC, et al. Early antiretroviral therapy is associated with lower HIV DNA molecular diversity and lower inflammation in cerebrospinal fluid but does not prevent the establishment of compartmentalized HIV DNA populations. PLoS Pathog. 2017;13:e1006112.
69. Deleage C, Schuetz A, Alvord WG, Johnston L, Hao X-P, Morcock DR, et al. Impact of early cART in the gut during acute HIV infection. JCI Insight. 2016;1:e87065 70.
70. Strain MC, Little SJ, Daar ES, Havlir DV, Gunthard HF, Lam RY, et al. Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. J Infect Dis. 2005;191:1410–8.
71. Phanuphak N, Teeratakulpisarn N, van Griensven F, Chomchey N, Pinyakorn S, Fletcher JL, et al. Anogenital HIV RNA in Thai men who have sex with men in Bangkok during acute HIV infection and after randomization to standard vs. intensified antiretroviral regimens. J Int AIDS Soc. 2015;18:19470.
72.•• Jain V, Hartogensis W, Bacchetti P, Hunt PW, Hatano H, Sinclair E, et al. Antiretroviral therapy initiated within 6 months of HIV infection is associated with lower T-cell activation and smaller HIV reservoir size. J Infect Di. 2013;208:1202–11. **Comparison of patients with early HIV infection who started ART early (<6 months) or later (≥ 2 years after infection) with at-risk HIV-negative controls for CD4+/CD8+ T cell activation and HIV reservoir size.**
73. Ananworanich J, Fauci AS. HIV cure research: a formidable challenge. J Virus Erad. 2015;1:1–3.
74. Herout S, Mandorfer M, Breitenecker F, Reiberger T, Grabmeier-Pfistershammer K, Rieger A, et al. Impact of early initiation of antiretroviral therapy in patients with acute HIV infection in Vienna. Austria PloS One. 2016;11:e0152910.
75. Hellmuth J, Colby D, Valcour V, Suttichom D, Spudich S, Ananworanich J, et al. Depression and anxiety are common in acute HIV infection and associate with plasma immune activation. AIDS Behav. 2017. doi:10.1007/s10461-017-1788-4.
76.•• Section Considerations for AntiretroviralUse in Special Patient Populations Acute and Recent (Early) HIV Infection. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed 8 Aug 2017 **The American guidelines.**
77. Wilson DP, Hoare A, Regan DG, Law MG. Importance of promoting HIV testing for preventing secondary transmissions: modelling the Australian HIV epidemic among men who have sex with men. Sex Health. 2009;6:19–33.
78. Frange P, Meyer L, Deveau C, Tran L, Goujard C, Ghosn J, et al. Recent HIV-1 infection contributes to the viral diffusion over the French territory with a recent increasing frequency. PLoS One. 2012;7:e31695.
79. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375:830–9.
80. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365:493–505.
81. Cohen MS, Smith MK, Muessig KE, Hallett TB, Powers KA, Kashuba AD. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? Lancet. 2013;382:1515–24.
82. Seng R, Rolland M, Beck-Wirth G, Souala F, Deveau C, Delfraissy J-F, et al. Trends in unsafe sex and influence of viral load among patients followed since primary HIV infection, 2000-2009. AIDS. 2011;25:977–88.
83. Dokubo EK, Shiraishi RW, Young PW, Neal JJ, Aberle-Grasse J, Honwana N, et al. Awareness of HIV status, prevention knowledge and condom use among people living with HIV in Mozambique. PLoS One. 2014;9:e106760.

84. Wertheim JO, Oster AM, Hernandez AL, Saduvala N, Bañez Ocfemia MC, Hall HI. The international dimension of the U.S. HIV transmission network and onward transmission of HIV recently imported into the United States. AIDS Res Hum Retrovir. 2016;32:1046–53.
85. Colafigli M, Torti C, Trecarichi EM, Albini L, Rosi A, Micheli V, et al. Evolution of transmitted HIV-1 drug resistance in HIV-1-infected patients in Italy from 2000 to 2010. Clin Microbiol Infect. 2012;18:E299–304.
86. Colby DJ, Crowell TA, Sirivichayakul S, Pinyakorn S, Kroon E, Benjapornpong K, et al. Declining trend in transmitted drug resistance detected in a prospective cohort study of acute HIV infection in Bangkok. Thailand J Int AIDS Soc. 2016;19:20966.
87. Ferreira ACG, Coelho LE, Grinsztejn E, de Jesus CS, Guimarães ML, Veloso VG, et al. Transmitted drug resistance in patients with acute/recent HIV infection in Brazil. Braz J Infect Dis. 2017;S1413-8670:30330-0.
88. Nozza S, Poli A, Ripa M, Galli L, Chiappetta S, Spagnuolo V, et al. Efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as treatment for primary or recent HIV infection. J Antimicrob Chemother. 2017;72:632–3.
89. Ngo Bell EC, Vandenhende M-A, Caldato S, Saunier A, Bellecave P, Tumiotto C, et al. High decay of blood HIV reservoir when tenofovir/emtricitabine/elvitegravir/cobicistat is initiated during the acute primary HIV infection. J Antimicrob Chemother 2017. doi:10.1093/jac/dkx166.
90. Chéret A, Nembot G, Mélard A, Lascoux C, Slama L, Miailhes P, et al. Intensive five-drug antiretroviral therapy regimen versus standard triple-drug therapy during primary HIV-1 infection (OPTIPRIM-ANRS 147): a randomised, open-label, phase 3 trial. Lancet Infect Dis. 2015;15:387–96.
91. Karris MY, Umlauf A, Vaida F, Richman D, Little S, Smith D. A randomized controlled clinical trial on the impact of CCR5 blockade with maraviroc in early infection on T-cell dynamics. Medicine. 2016;95:e5315.
92. Ripa M, Pogliaghi M, Chiappetta S, Nozza S, Soria A, Coppalini G, et al. Maraviroc in addition to cART during primary HIV infection: results from MAIN randomized clinical trial and 96-weeks follow-up. J Clin Virol. 2016;85:86–9.
93. Knox DC, Anderson PL, Harrigan PR, Tan DHS. Multidrug-resistant HIV-1 infection despite preexposure prophylaxis. N Engl J Med. 2017;02; 376(5):501–2.